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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,609	10/23/2003	Sabine Short	07414.0075-00000	6477

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EXAMINER	
BABIC, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,609	SHORT ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-9,12-17,26 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-9,12-17,26 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. 9/15/06
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1, 6-9, 12-17, 26, 52 are pending. The following Office Action is in response to Applicant's response dated July 11, 2006.

Sequence Rules Compliance

In view of Applicant's amendment to the specification, the instant application now compliés with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures set forth in 37 C.F.R. §§ 1.821-1.825

Specification

The objection to the abstract has been withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 6-9, 12-17, and 26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (U.S. 6,027,889) in view of Wittwer et al. (U.S. 6,303,305), in further view of Godfrey et al. "Quantitative mRNA Expression Analysis from Formalin-Fixed, Paraffin-Embedded Tissues Using 5' Nuclease Transcription-Polymerase Chain Reaction" Journal of Molecular Diagnostics. 2000. Vol. 2, No. 2: Pages 84-91).

With regard to claim 1 as amended, Barany et al. teach a method (Figures 8-12; Columns 9-11; Columns 23-30; Column 41, Example 4, for example) comprising: forming a ligation reaction composition comprising the sample, and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the target-specific portions, and the 3' primer-specific portion (Figures 8-12; Columns 9-11; Columns 23-30; Column 41, Example 4, for example).

With specific regard to the amendments to claim 1 presented in Applicant's response dated July 11, 2006, an interview was held with Andrew Finn on September 15 in which Applicant's representative pointed the Examiner to where the amended claim was believed to differ from the teachings of Barany. Applicant specifically pointed to claim 1, line 15 as amended wherein the claim requires that at least one primer specific portion of the two probe sets probe sets (i.e. 5' or 3') has a different sequence from one another. It is submitted that Barany does teach multiple probe sets that have a different primer specific portion. Applicant is directed to figures 15 and 17 as well as columns 27 and 28 wherein Barany expressly teaches two probe sets that contain different primer specific portions (figure 15, step 1, for example) for the purpose of distinguishing two different polymorphisms (figure 15, steps 2-4, for example).

Barany further teaches identifying one or more of a plurality of sequences, differing by one or more single-base (i.e. SNPs), in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example). They further disclose one or more oligonucleotide probe sets (Column 23, Lines 15-35, for example). They further disclose one or a plurality of oligonucleotide primer sets (Column 23, Lines 25-30, for example). It is submitted that Barany clearly teaches the detection of multiple target sequences of different sequence structure utilizing a plurality of probe sets of different sequence structure.

Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12, 15, 17; Columns 24,25, for example), however, does not expressly

disclose employing real-time detection methods using double stranded dependent labels, or detection through comparing threshold values.

Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded dependent labels (Column 10, Example 2, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels, since Wittwer and Godfrey suggest such a modification. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular

allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claim 6, Barany et al. disclose identifying one or more of a plurality of sequences, differing by one or more single-base, in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example).

With regard to Claim 7, Barany et al. disclose a method for detecting the presence or absence of at least one target nucleic acid sequence in a sample (Figures 8-12; Columns 9-11; Columns 23-30; Column 41, Example 4, for example) comprising: forming a ligation reaction composition comprising the sample, and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising

the 5' primer-specific portion, the target-specific portions, and the 3' primer-specific portion; forming at least one amplification reaction composition comprising: at least a portion of the test composition, a polymerase, a double-stranded-dependent label; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product.

Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12; Columns 24,25, for example), however, does not expressly disclose employing real-time detection methods using double stranded dependent labels, or detection through comparing threshold values.

Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded dependent labels (Column 10, Example 2, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation

dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels, since Wittwer and Godfrey suggest such a modification.. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 8 and 9, Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3, Lines 16-51, for example) and threshold time values (T_t) (Column 2, Lines 38-45, for example) with double stranded dependent labels (Column 10, Example 2, for example).

With regard to Claims 8, 12, 13, and 14, Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold cycle values (C_t) (Column 3,

Lines 16-51, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods using double-stranded dependent labels, since Wittwer and Godfrey suggest such a modification.. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from double-stranded dependent labels. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Wittwer et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie*

obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 9, 15, 16, and 17, Wittwer et al. discloses methods for nucleic acid detection comprising determining threshold time values (T_t) (Column 2, Lines 38-45, for example). Wittwer et al. does not expressly disclose the comparison of threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example). Godfrey et al. do not expressly disclose comparison of threshold time values (T_t), however, it would have been obvious to one of ordinary skill in the art that the comparison of any threshold value, whether as a function amplification time or cycle, would have yielded identical results. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claim 26, Barany et al., who teaches identifying one or more of a plurality of sequences, differing by one or more single-base (i.e. SNPs), in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example). They further disclose one or more oligonucleotide probe sets (Column 23, Lines 15-35, for example). They further disclose one or a plurality of oligonucleotide primer sets (Column 23, Lines 25-30, for example).

2. Claim 52 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (U.S. 6,027,889) in view of Barany et al. (U.S. 6,312,892).

The methods of Barany et al. ('889) have been outlined in the above rejections. Barany et al. ('889) do not expressly disclose the incorporation of nucleotide analogues.

Barany et al. ('892) discloses the above LDR/PCR methods with the use of nucleotide analogues (Figure 9; Column 33, Line 45-Column 34, Line 25, for example). They expressly disclose use of a nucleotide analogue to reduce the amount ligation formed off minority mutant targets, and thus, not overwhelming the signal (Column 34, Lines 1-25, for example). Barany et al. ('892) does not expressly disclose the use of poly-deoxy-inosinic-deoxy-cytidylic acid, however, they disclose several representative nucleotide analogues, including inosine-based analogues.

Based on the combined disclosures of the applied references, it would have been obvious to one of ordinary skill in the art to modify the LDR/PCR methods of Barany et al. to incorporate nucleotide analogues such as poly-deoxy-inosinic-deoxy-cytidylic acid. The motivation to do so, provided by Barany et al. ('892), would have been to reduce the amount ligation formed off minority mutant targets. At the time of invention, the disclosure of Barany et al. ('892) clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

Response to Arguments - Claim Rejections - 35 USC § 103

Applicant's arguments with respect to the previously applied references have been fully considered but they are not persuasive.

Rejection of claim(s) 1, 6-9, 12-17, and 26 over Barany in view of Wittwer and Godfrey

Applicant asserts that neither Barany, nor the combination of references teaches or suggests the features of claim 1. Applicant provides no supporting arguments as to what specific features fail to be taught or suggested by the applied references.

An interview was held with Andrew Finn on September 15 in which Applicant's representative pointed the Examiner to where the amended claim was believed to differ from the teachings of Barany. Applicant specifically pointed to claim 1, line 15 as amended wherein the claim requires that at least one primer specific portion of the two probe sets probe sets (i.e. 5' or 3') has a different sequence from one another. It is submitted that Barany does teach multiple probe sets that have a different primer specific portion. Applicant is directed to figures 15 and 17 as well as columns 27 and 28 wherein Barany expressly teaches two probe sets that contain different primer specific portions (figure 15, step 1, for example) for the purpose of distinguishing two different polymorphisms (figure 15, steps 2-4, for example).

Barany further teaches identifying one or more of a plurality of sequences, differing by one or more single-base (i.e. SNPs), in a plurality of target nucleotide sequences (Column 23, Lines 10-20, for example). They further disclose one or more

oligonucleotide probe sets (Column 23, Lines 15-35, for example). They further disclose one or a plurality of oligonucleotide primer sets (Column 23, Lines 25-30, for example). It is submitted that Barany clearly teaches the detection of multiple target sequences of different sequence structure utilizing a plurality of probe sets of different sequence structure.

Thus, the rejections are maintained.

Rejection of claim(s) 52 over Barany ('889) in view of Barany ('892)

Please refer to the response above.

Claims 1, 6-9, 12-17, and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-10 of copending application Aydin (10/666806).

Aydin recites a method for detecting at least one target nucleic acid sequence in a sample comprising: forming a ligation reaction composition comprising the sample and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target nucleic acid sequence, and wherein one probe in each probe set

further comprises an addressable portion located between the primer-specific portion and the target-specific portion, wherein the addressable portion comprises a sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the target-specific portions, the addressable portion, and the 3' primer-specific portion; forming an amplification reaction composition comprising: the test composition; a polymerase; a labeled probe, wherein the labeled probe has a first detectable signal value when it is not hybridized to a complementary sequence, and wherein the labeled probe comprises the sequence of the addressable portion or comprises a sequence complementary to the sequence of the addressable portion; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product; subjecting the amplification reaction composition to at least one amplification reaction; and detecting a second detectable signal value at least one of during and after the amplification reaction, wherein a threshold difference between the first detectable signal value and the second detectable signal value indicates the presence of the target nucleic acid sequence, and wherein no threshold difference between the first detectable signal value and the second detectable signal value indicates the absence of the target nucleic acid sequence.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to the same general inventive concept of detecting a target nucleic acid comprising a ligation detection reaction further comprising detecting threshold difference of detectable signals wherein the only differences between the conflicting claims are: 1) in the instant claims, the incorporation of a second probe set to detect multiple different targets; and 2) in the claims of Aydin, the incorporation of a labeled detection probe. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to incorporate these modifications.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1, 6-9, 12-17, 26, 52 are rejected. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Iannone et al. ("Multiplexed single nucleotide polymorphism genotyping by oligonucleotide ligation and flow cytometry" Cytometry. 2000 Feb 1;39(2):131-40).

Iannone teaches multiplexed SNP genotpying utilizing an oligonucleotide ligation assay that utilizes probes with ZipCode sequences (i.e. allele specific sequence portions).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9/15/2006

Christopher M. Babic
Patent Examiner

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

9/18/06